ARIC Manuscript Proposal # 1459

PC Reviewed: 12/9/08   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: **Cardiac autonomic imbalance and incident atrial fibrillation: the Atherosclerosis Risks in Communities study**

   b. Abbreviated Title: **Autonomic imbalance and AF**

2.   Writing Group:

Sunil K. Agarwal MD MPH , Alvaro Alonso, MD PhD , Elsayed Z. Soliman MD MSc MS, Alanna Chamberlain MPH, Marietta Ambrose MD, Ross J. Simpson MD PhD, Gerardo Heiss MD PhD

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _SKA_ **[please confirm with your initials electronically or in writing]**

First author: **Sunil K. Agarwal**
Address: Department of Epidemiology, CVD Program, University of North Carolina at Chapel Hill, 137 E Franklin St, Bank of America, Suite 32, Chapel Hill, NC 27514
Phone: (919) -265 -4727. Fax: (919)-966-9800. E-mail: sunilagarwal1@gmail.com

ARIC author: **Alvaro Alonso**
Address:1300 S 2nd St, Suite 300. Minneapolis, MN 55454
Phone: +16166268597. Fax: +16126240315. Email: aalogut@alumni.unav.es

3.   Timeline: Within 15 months following proposal's acceptance.

4.   Rationale:
Atrial Fibrillation (AF), a commonly seen sustained arrhythmia in clinical practice, is associated with incident stroke, heart failure and mortality[1].

Pure autonomic initiation of clinical AF is uncommon and seen only in situations of high sympathetic or high vagal tone, but recordings of heart rate variability (HRV) disclose autonomic perturbations in some patients that precede the onset of AF[1]

Further, in canine models, preliminary results show that simultaneous sympatho-vagal discharges precede the onset of Paroxysmal Atrial Fibrillation[2]. Vagal denervation concomitant with extensive endocardial catheter ablation was associated with significant reduction in subsequent AF in a third of 297 patients with paroxysmal AF[3].

The noninvasive measurement of autonomic tone in humans has been augmented by measures of HRV[4], which reflect changes in the relative autonomic modulation of heart rate rather than the absolute level of sympathetic or parasympathetic tone. Although, an imbalance in the autonomic tone was shown to be a precursor of AF initiation, study results show that both a higher or a lower vagal-sympathetic tone may act as precursor depending on other substrates[2].
In addition to measures of HRV, another prevalent, and possibly informative measure of autonomic dysfunction is postural hypotension (5% at the ARIC baseline).

A single published report, using data from the Framingham Heart Study has looked at the association of HRV with incident AF in a general population[5]. This study reported a postivie association (gender and age adjusted) between one of the HRV measure and incident AF. The association was attenuated, becoming statistically not-significant after adjustment for CVD risk factors. Low study power (only 132 subjects, out of 2576, had incident AF), and non representation of blacks were important limitations. The ARIC study provides an opportunity to evaluate the association between HRV measures (baseline), and postural hypotension (as proxies of autonomic function) with the incidence of AF in a large cohort of blacks and whites men and women.

5. **Main Hypothesis/Study Questions**:

Autonomic imbalance, measured using various measures of heart rate variability, and postural hypotension is associated with incident atrial Fibrillation.
        This association is seen across race and gender.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

We will use time to event analysis using Cox proportional hazards models to estimate the association of various available short-term heart rate variability measures at ARIC baseline visit using 2 minutes ECG record with incident atrial fibrillation.

Exclusions: Participants with either missing or poor heart rate variability measures at baseline, and prevalent AF (identified from ECGs at baseline), other electrical abnormalities in heart rhythm (such as advanced AV blocks, pacemakers, wandering atrial beats, supra-ventricular or ventricular tachycardia).

Outcome: Incidence of AF, diagnoses will be obtained from three sources: ECGs at the three follow-up study exams as described by Soliman et al, (Stroke 2008 in press (ARIC MS 1156)) , and hospital discharge records and death certificates as described by Alonso et al (unpublished ARIC MS # 1351) will be the main endpoint. In brief, hospital discharge AF was defined as the presence of ICD-9 code 427.31 in the discharge codes. Patients with a diagnosis of atrial flutter (ICD-9 code 427.32) not developing AF in subsequent follow-up were not considered cases. AF hospitalization diagnoses occurring

simultaneously with heart revascularization surgery (ICD-9 code 36.X) or other cardiac surgery involving heart valves or septa (ICD-9 code 35.X), without evidence of AF during subsequent hospitalizations or study exams were excluded.

Primary exposure: Cardiac autonomic dysfunction will be estimated from heart rate variability measures collected at baseline (visit 1), as described in previous ARIC publications, specifically, we will use:
- Mean normal-to-normal R-R interval length (RR)
- Standard deviation of normal-to-normal R-R intervals (SDNN)
- Root mean square of successive differences in normal-to-normal R-R intervals (RMSSD)
- High frequency and low frequency spectral components, and low to high frequency ratios. All exposures will be categorized in quartiles and linearity assumptions assessed.

Secondary exposure: Postural hypotension: defined as a decrease of 20 mm Hg in systolic blood pressure or a decrease of 10 mm Hg in diastolic blood pressure on standing at ARIC baseline.

Covariates: Previously identified risk factors for AF, also having influence on HRV: age, sex, race-center, body mass index, physical activity, diabetes, hypertension, ECG-defined left ventricular hypertrophy, smoking, prevalent MI, prevalent HF. Also, education and/or income as measures of socioeconomic status.

Methodological limitations: The quality of HRV data may be poor in a substantial proportion of cohort at baseline (>25%), thus leading to many exclusions. We don't have reasons to assume that exclusion is differential in terms of study outcome, and also similar exclusions have been used in previous studies using this data. We will additionally use HRV data obtained at visit 4 (6 min) and incident AF subsequent to visit to examine the consistency of observed results. Also, we will explore the association of short EKG derived time domain measures of HRV (as there are very few exclusions) with incident AF.

Multiple hypothesis testing is a concern because of various measures of HRV. HRV measures are highly correlated thus a conservative correction such as Benferroni's is not required. We will however consider this limitation while interpreting the results.

7.a. Will the data be used for non-CVD analysis in this manuscript?   No
b. NA

8.a. Will the DNA data be used in this manuscript? No

8.b. and 8.c NA

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and

**previously approved manuscript proposals either published or still in active status.
No**

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

MS # 1156: Electrocardiographic Prediction of AF: the ARIC Study
MS # 1351: Incidence of atrial fibrillation in a bi-racial cohort: the ARIC study
MS # 1389: Metabolic Syndrome and Risk of Incident AF: the ARIC study
MS # 1433: Serum uric acid and the risk of AF: the ARIC study

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?   Yes

11.b. If yes, is the proposal
   __X_   A. primarily the result of an ancillary study (list number* _2008.09_)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.
   The writing team is aware of this

Reference:
1.   Fuster, V., et al., *ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation).* J Am Coll Cardiol, 2006. **48**(4): p. 854-906.
2.   Chen, P.S. and A.Y. Tan, *Autonomic nerve activity and atrial fibrillation.* Heart Rhythm, 2007. **4**(3 Suppl): p. S61-4.
3.   Pappone, C., et al., *Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation.* Circulation, 2004. **109**(3): p. 327-34.
4.   *Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.* Eur Heart J, 1996. **17**(3): p. 354-81.
5.   Singh, J.P., et al., *Is baseline autonomic tone associated with new onset atrial fibrillation?: Insights from the framingham heart study.* Ann Noninvasive Electrocardiol, 2004. **9**(3): p. 215-20.